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Clinical Manifestations in 105 Persons With Nevoid Basal Cell Carcinoma Syndrome

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Nevoid basal cell carcinoma syndrome (NBCC; Gorlin syndrome), an autosomal dominant disorder linked to 9q22.3-q31, and caused by mutations in PTC, the human homologue of the *Drosophila patched* gene, comprises multiple basal cell carcinomas, keratocysts of the jaw, palmar/plantar pits, spine and rib anomalies and calcification of the falx cerebri. We reviewed the findings on 105 affected individuals examined at the NIH since 1985. The data included 48 males and 57 females ranging in age from 4 months to 87 years. Eighty percent of whites (71/90) and 38% (5/13) of African-Americans had at least one basal cell carcinoma (BCC), with the first tumor occurring at a mean age of 23 (median 20) years and 21 (median 20) years, respectively. Excluding individuals exposed to radiation therapy, the number of BCCs ranged from 1 to >1,000 (median 8) and 1 to 3 (median 2), respectively, in the 2 groups. Jaw cysts occurred in 78/105 (74%) with the first tumor occurring in 80% by the age of 20 years. The number of total jaw cysts ranged from 1 to 28 (median 3). Palmar pits and plantar pits were seen in 87%. Ovarian fibromas were diagnosed by ultrasound in 9/52 (17%) at a mean age of 30 years. Medulloblastoma occurred in 4 patients at a mean age of 2.3 years. Three patients had cleft lip or palate. Physical findings include "coarse face" in 54%, relative macrocephaly in 50%, hypertelorism in 42%, frontal bossing in 27%, pectus deformity in 13%, and Sprengel deformity in 11%. Important radiological signs included calcification of the falx cerebri in 65%, of the tentorium cerebelli in 20%, bridged sella in 68%, bifid ribs in 26%, hemivertebrae in 15%, fusion of the vertebral bodies in 10%, and flame shaped lucencies of the phalanges, metacarpal, and carpal bones of the hands in 30%. Several traits previously considered components of the syndrome (including short fourth metacarpal, scoliosis, cervical ribs and spina bifida occulta) were not found to be significantly increased in the affected individuals. This study delineates the frequency of the clinical and radiological anomalies in NBCC in a large population of US patients and discusses guidelines for diagnosis and management. Am. J. Med. Genet. 69:299–308, 1997.

KEY WORDS: nevoid basal cell carcinoma syndrome (NBCC); basal cell carcinoma; keratocyst; pitting; ovarian fibroma; medulloblastoma; clinical features; radiological features; probands

INTRODUCTION

NBCC is an autosomal dominant disorder with an estimated prevalence of 1 in 57,000 [Farndon et al., 1992] to 1 in 164,000 [Shanley et al., 1994]. The gene has been mapped to 9q 22.3-q31 [Gailani et al., 1992; Farndon et al., 1992; Reis et al., 1992] with no evidence for heterogeneity [Chenevix-Trench et al., 1993; Wicking et al., 1994; Compton et al., 1994; Goldstein et al., 1994]. Recently, mutations in the human homologue of

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Drosophila *patched,* PTC, have been found to cause NBCC [Hahn et al., 1966; Johnson et al. 1996]. The gene is highly penetrant, but there is wide variation in the expressivity [Anderson et al., 1967]. The syndrome comprises multiple basal cell carcinomas, or early onset of BCC (i.e. one BCC prior to the age of 20 yr), keratocysts of the jaw, palmar/plantar pits, calcified dural folds, spine and rib anomalies, and characteristic face [Howell and Caro, 1958; Gorlin and Goltz, 1960]. The BCCs, which vary from a few to thousands, exhibit a wide range of appearance clinically and histopathologically, usually first appear around puberty and usually involve the face, back and chest. There is a difference in the frequency of BCCs between whites and African-Americans with NBCC [Goldstein et al., 1994]. Odontogenic keratocysts develop in more than 50% of NBCC patients often in the first decade. The cysts occur in both jaws and are lined by a thin layer of stratified squamous epithelium resulting in their designation as keratocysts. A well known trait is their recurrence estimated at 6 to 60% after enucleation of the keratocysts. Recurrence is partly attributed to the presence of satellite cysts [Dominguez and Keszler, 1988]. The plantar and palmar pits appear as shallow depressions which are due to partial or complete absence of the stratum corneum; they are found on the hands and feet, mainly on the palms and soles, but they can also be demonstrated on the sides, web spaces and dorsum of the fingers and toes [Howell and Mehregan, 1970].

On the basis of over 250 reports in the literature, Gorlin et al. [1963, 1965, 1971, 1972, 1987, 1995] identified several additional anomalies in the NBCC syndrome as listed in Tables I and V. Additionally radiological signs reported by several authors [Anderson et al., 1967; McEvoy and Gatzek, 1969; Dunnick et al., 1978] are listed in Table III. Individuals are prone to several specific neoplasms such as medulloblastoma [Herzberg and Wiskemann, 1963; Evans et al., 1991], other CNS tumors such as meningioma [Tamoney, 1969; Gorlin, 1987], ovarian fibroma which are often bilateral [Clendenning et al., 1963], and cardiac fibroma [Littler, 1979; Jones et al., 1986; Lacro and Jones, 1987; Coffin, 1992].

Two recent studies, one from the UK [Evans et al., 1993] and the other from Australia [Shanley et al., 1994], have reported the frequency of the manifestations in large series of NBCC patients. In our cross-sectional study of NBCC from the US population reported here we make comparisons between the frequency of the clinical and radiological signs in individuals with NBCC and their unaffected relatives to delineate the phenotype of NBCC.

METHODS

Patients were recruited to the National Institutes of Health for participation in a clinical and gene linkage study beginning in 1985. The study was approved by the Institutional Review Board and patient consent was obtained. For purposes of recruitment for this study, criteria used for diagnosis of NBCC syndrome were the presence of 2 major, or one major and 2 minor criteria. The major criteria used included multiple BCCs or one BCC before 20 years, keratocysts of the jaw, palmar/plantar pits, lamellar calcification of the falx cerebri on skull radiograph, rib anomalies (bifid, synostosed, hypoplastic), ovarian fibroma, medulloblastoma, flame shaped lucencies in the phalanges, and brachymetacarpaly in the 4 limbs. Minor criteria included spina bifida occulta or other vertebral anomalies, brachymetacarpaly in at least one limb, hypertelorism or telecanthus, and frontal bossing. A diagnosis was also established by the presence of a first degree relative with NBCC and one major or two minor criteria.

We evaluated 20 multiple case families and 6 cases in which family history was negative. We also obtained clinical information on 105 individuals who fulfilled the criteria for NBCC and on 73 unaffected first degree relatives and 28 spouses. Patients underwent physical, dermatological, dental, and radiological examinations. Medical and family history were also obtained. Scoring of palmar and plantar pits was done on a scale of 0 to 3 (none, few, moderate, many). Dental evaluation included a panorex film. Radiological studies included anteroposterior (AP) chest, rib, spine, AP and lateral skull, hand and foot, long bones, and pelvis films. CT or MRI studies of the brain were obtained on 42 affected individuals (37 CT, 5 MRI) and 2 unaffected relatives had MRI studies. Ultrasound exam for ovarian fibromas was performed in 52 affected females and 37 unaffected females. All radiographs were reviewed by a single radiologist (BP).

Macrocephaly relative to height was determined by the formula of Bale et al. [1991] and the presence of telecanthus and hypertelorism by the method of Feingold and Bossert [1974].

Statistical Analysis

Statistical analysis was performed using SPSS 6.1 for Windows (SPSS Inc., Chicago, Illinois). Crosstabulation analysis of the relationship between the recorded categorical variables (such as absence or presence of the various clinical features) by groups was performed using the Crosstabs procedure. Statistical differences between the observed and expected values in each group were tested using the Pearson chi-square test.

Comparison of the means of height, head circumference and eye measurements in the 3 groups was done using the analysis of variance (ANOVA) procedure.

The distribution of time to occurrence of the first BCC or jaw cyst in the affected individuals was performed using Kaplan-Meier Survival Analysis. Individuals who had not experienced an event (i.e. developed tumors) at the age of last observation or who did not survive long enough to develop tumors were censored. Statistical comparison between the whites and African-Americans was done using the Log-Rank test.

Imprinting

The effect of genomic imprinting, defined as differential expression of a gene depending on the sex of the parent who transmits it [Hall, 1990] was assessed. We compared the frequency of the various manifestations

of NBCC in affecteds who had inherited the disorder from their fathers (N = 48) versus those who had inherited it from their mothers (N = 36). Cross-tabulation analysis of the manifestations versus the parental transmission group was performed and statistical significance tested using the Pearson chi-square test.

Anticipation

The observation of increased severity of a disease phenotype in successive generations within the same family is known as anticipation [Sutherland and Richards, 1992]. We evaluated the data for the presence of anticipation as follows: Significant differences between generations was evaluated by performing a chi-square test of the frequency of structural anomalies in each generation. Each parent-child comparison was assessed independently. A parent with several children was included as many times as the number of children in the analysis. A total of 63 affected parent-child pairs was analyzed. The ages at first BCC or jaw cyst were not evaluated because of possible earlier ascertainment in younger generations.

RESULTS

The age range of the 105 affected persons was 4 months to 87 years (mean 34.5 yrs.). There were 48 males and 57 females (ratio 1:1.2) who fulfilled the criteria for NBCC. The 73 unaffected individuals ranged in age from 5.5 to 78 (mean 32) years. The male to female ratio of the unaffected individuals was 1:1.8. The status of 3 individuals (2 males and one female) was considered to be 'indeterminate' as they only partially met the diagnostic criteria for NBCC (i.e first degree relative and one minor feature). Their ages were 5.2, 17 and 34 years. The spouses ranged in age from 20 to 87 (mean 47) years and their sex ratio was 1:1.5. Eighty-six percent (90/105) of the affected population was white, 13% (13/105) African-American and 2% (2/105) was Mexican/Asian.

SKIN FINDINGS

Basal Cell Carcinomas

Of the total population, 77 individuals had BCCs either by history or first noted at the time of their NIH evaluation. The age of first diagnosis of BCCs ranged from 3 to 53 years (mean 21.4 years, median 20 years). BCCs were seen mainly on the face but also on the trunk and limbs. The appearance of the BCCs ranged from small milia around the eyes and nose to large aggressive tumors. The data on BCCs in individuals with NBCC was analyzed separately for whites and African-Americans. In the whites, 80% (71/90) were noted to have one or more BCCs either at the time of examination or by previous report. The number of previous BCCs reported in whites ranged from 1 to >1,000 (mean 62, median 8). Most of the individuals who had developed BCCs reported multiple lesions by the time they were evaluated; the only affected individuals in whom a solitary BCC was documented were either African-American or under age 21 years. Among the Caucasians no correlation was found between the skin type and the age of onset of first BCC or the total number of BCCs reported. Among the African-Americans, only 38% (5/13) developed one or more BCCs. One of the African-American probands was a male who had medulloblastoma treated by radiotherapy at age 2 years [Korczak et al., 1997]. At the time of evaluation at 6.5 years he had approximately 100 BCCs in the radiation field. In the remaining 4 African-Americans the total number of BCCs ranged from 1 to 3 with the first BCC occurring between the ages of 14 and 27 years. Our data included a 6.5 yr old Mexican-Asian male who had developed approximately 200 BCCs first diagnosed at age 6 years. His 44 year old father had moderate bilamellar falx calcification and hemivertebra of the fourth thoracic vertebra, but no other clinical manifestation of NBCC.

Figure 1 shows the frequency of BCCs in whites at different ages with 97% over age 40 years having developed BCCs. A Kaplan-Meier lifetable analysis of the age at first BCC showed significantly different probabilities of developing BCCs at different ages in whites vs. African-Americans (Log-Rank test, P = 0.001). A probability curve of the risk of developing BCCs at specific ages is shown in Figure 2. Approximately 50% of affected whites developed their first BCC by the age of 21.5 years and 90% by 35 years. By contrast, in African-Americans there was approximately a 20% and 40% probability of developing BCCs at these ages, respectively.

One BCC was also found on examination of, or reported previously by, 2/73 unaffected individuals at ages 44 and 55 years. These individuals did not fulfill the criteria for diagnosis of NBCC as they had no other signs of NBCC and did not develop their BCCs prior to 20 years of age. One female developed two BCCs at age 65 years. This individual did not have any other findings of NBCC and subsequent genetic linkage studies confirmed that she had not inherited the gene for NBCC.

Radiation therapy for medulloblastoma administered in 3 individuals was associated with early development of BCCs in the radiation fields. These persons in whom BCCs occurred at ages 6, 9 and 12 years, developed BCCs significantly earlier than the overall

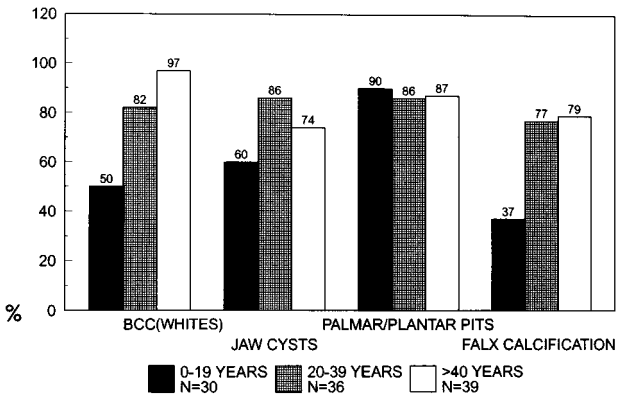

Fig. 1. Frequency of the major clinical signs: BCCs, jaw cysts, palmar/plantar pits and calcification of the falx cerebri in the different age groups: 0–19 years, 20–39 years and ⩾40 years.

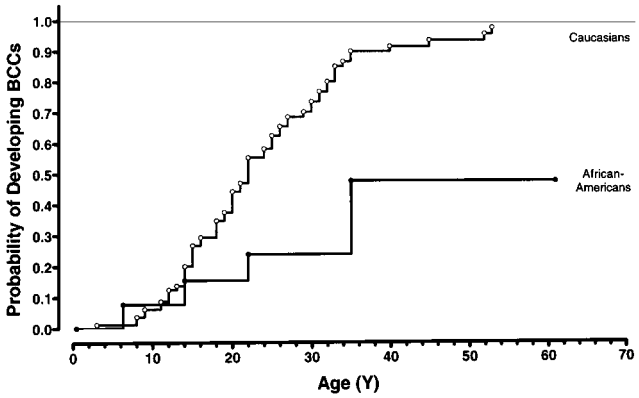

Fig. 2. A probability curve of the risk of developing BCCs at different ages in NBCC, in Caucasians versus African-Americans.

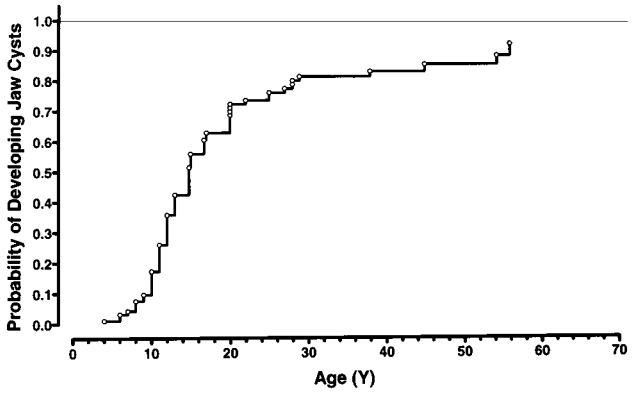

Fig. 3. A probability curve of the risk of developing jaw cysts at different ages among all patients with NBCC. There was no difference between African-Americans and Caucasians.

mean of 21.3 years in the entire sample ($P = 0.03$). One of these individuals developed BCCs which invaded the dura and caused his death at the age of 45 years. A 6.5-year-old African-American male had approximately 100 BCCs in the radiation field when examined at the NIH at the age of 6.5 years. The third case was a 26-year-old male who developed hundreds of BCCs over his back in the radiation field at the age of 12 years. Two individuals who received radiation for facial BCCs developed aggressive BCCs in the radiation fields. One female who received radiation for a 'birthmark' on the perineum in infancy was noted to have perineal BCCs at the age of 29 years.

Palmar and Plantar Pits

Pits were seen in 87% (89/102) of affected individuals in the palms and/or the soles. Palmar pits occurred in 86% (88/102), and plantar pits in 81% (79/97). Seventy-seven percent had palmar and plantar pits. Pitting of the palms was seen at approximately the same frequency in all age groups (Fig. 1). The youngest individual in whom pits were observed was 5 months old. Approximately 20% of children under the age of 10 years did not have visible pits on examination. Of individuals with pits, 51% had few pits, 28% had a moderate number of pits and 20% had many pits. Pitting was not observed in 13/102 (13%); these individuals ranged in age from 4 months to 61 years.

One unaffected individual was noted to have a single pit on a palm, and one spouse was noted to have two faint palmar pits. No unaffected individual was noted to have >3 pits.

JAW CYSTS

Seventy-eight of 105 (74%) individuals with NBCC had a history of jaw cysts or a jaw cyst detected on dental evaluation at the NIH. The age of onset of the jaw cysts ranged from 4 to 67 years (mean 17.1 years, median 13 years). The number of jaw cysts ranged from 1 to 28 (mean 5.1, median 4.5). Five individuals had more than 10 jaw cysts in their lifetime. The Kaplan-Meier life table analysis showed that the onset of jaw cysts correlated with the age of the patient; however, 75% developed jaw cysts by the age of 20 years (Fig. 3). One affected individual was found to have an ameloblastoma. No unaffected individual or spouse had jaw cysts.

MEDULLOBLASTOMAS

Four individuals had a medulloblastoma diagnosed between the ages of 2 and 3 years. Radiotherapy for the medulloblastoma had a marked effect on the early development of BCCs and other cerebral tumors. One girl died at 5 years from increased intracranial pressure due to secondary cerebellar ependymoma development. One of the 3 surviving individuals was a 25 year old man who, in addition to developing hundreds of BCCs in the radiation field, developed neurological symptoms at the age of 26 years. MRI demonstrated several meningiomas, one of which was compressing his brain stem.

GENITOURINARY ANOMALIES

Fifty-two of the women and girls with NBCC were evaluated by pelvic ultrasound examination; 9 were found to have ovarian fibromas (17%). Their age ranged from 16 to 45 years (mean 30.6 years). Of women over the age of 30 years, 5/27 (18.5%) had ovarian fibromas detected by ultrasound. One woman with NBCC had a septate uterus. In none of the 37 unaffecteds who had pelvic ultrasound evaluation was an ovarian fibroma detected.

Among males, one affected and one unaffected (unrelated) individual had hypospadias. Four affected and one unaffected male had a history of cryptorchidism at birth. Three of these cases occurred in the same family—a father and son who both had NBCC and an unaffected son. All 3 had unilateral cryptorchidism requiring surgery.

PHYSICAL CHARACTERISTICS

Table I presents the physical findings for the 3 groups of relatives. Many cranio-facial anomalies were significantly more prevalent among the persons with NBCC. A metacarpal sign, previously associated with NBCC, was not found to be significantly increased in

TABLE 1. Frequency of Clinical Signs in Affected Individuals With NBCC Syndrome, Their Unaffected Relatives and Spouses

	Affected (%)	Unaffected (%)	Spouses (%)	*P*
Craniofacial anomalies				
Frontal bossing	27/103 (26)	0/68 (0)	1/25 (4)	<0.01
Skull shape abnormalities[a]	16/102 (16)	3/68 (4)	0/25 (0)	0.05
Macrocephaly-males >20 yr.[b]	15/28 (54)	2/16 (13)	1/11 (9)	0.01
Macrocephaly-females >20 yr.[b]	18/39 (46)	3/28 (11)	3/14 (21)	0.01
"Coarse face"	53/101 (52)	1/68 (2)	0/24 (0)	<0.01
Epicanthic folds	17/102 (17)	9/68 (13)	2/24 (8)	0.54
Synophrys	35/102 (34)	12/68 (17)	2/24 (8)	<0.01
Ear pits	6/70 (9)	2/49 (4)	0/23 (0)	0.25
Eye anomalies				
Strabismus	19/101 (19)	1/68 (2)	1/25 (4)	<0.01
Hypertelorism[c]	41/98 (42)	6/49 (12)	1/25 (4)	<0.01
Telecanthus[c]	25/97 (26)	6/49 (12)	2/25 (8)	0.04
Oropharyngeal anomalies				
Cleft palate	3/105 (3)	0/73 (0)	0/25 (0)	<0.01
Other palate abnormalities[d]	47/102 (46)	11/66 (20)	0/23 (0)	<0.01
Skeletal anomalies				
Pectus deformities	12/98 (12)	0/58 (0)	0/15 (0)	0.02
Sprengel deformity	11/101 (11)	0/61 (0)	0/16 (0)	0.03
Metacarpal sign[e]	10/99 (10)	4/69 (6)	0/23 (0)	0.19
Syndactyly	24/102 (24)	3/65 (5)	1/22 (5)	0.19

[a]Dolichocephaly and brachycephaly.
[b]Bale et al., 1991.
[c]Feingold and Bossert, 1974.
[d]High-arched palate or prominent palatine ridges.
[e]Short 4th metacarpal- unilateral/bilateral.

the affected group. Ten percent of affected and 6% of unaffected persons, but none of the spouses, had definite unilateral or bilateral short fourth metacarpals.

Physical Measurements

Mean values of the physical measurements in the 3 groups were analyzed in individuals over the age of 18 years. Males and females were considered separately (Table II). The mean height and lower body segment were significantly increased in the affected group compared to the unaffected or spouse group. The upper/lower body segment ratio was normal in the affected individuals indicating that they were proportionately taller individuals rather than having disproportionately long limbs. Using the formula of Bale et al. [1991], the head circumference 2 standard deviations above the mean (95th centile) was calculated in adults over the age of 20 years standardized to gender and height. Relative macrocephaly was present if the observed head circumference exceeded the predicted head circumference. Relative macrocephaly was observed at a higher frequency in affected (50%) compared to unaffected individuals ($P = 0.01$) (Table I).

Eye measurements showed that 42% in the affected group were hyperteloric (interpupillary distance >2SD from the mean). Telecanthus (inner-canthal distance >2 SD from the mean), related to hypertelorism was seen more frequently in the affected population.

RADIOLOGICAL FINDINGS

Table III presents the radiological signs evaluated in the affected and unaffected persons.

Skull Radiographs

Calcification of the falx cerebri was observed in 65% of all affected individuals. Figure 1 shows that 23/29 (79%) individuals over the age of 40 years had falcial calcification, 20/26 (77%) between the ages of 20 and 40 years and 10/27 (37%) individuals under the age of 20 years. Faint calcification of the falx was seen in 2 unaffected males over 50 years. Neither had any other signs of NBCC. Calcification of the tentorium cerebelli and bridging of the sella turcica was also observed more frequently in the affected individuals.

Chest and Rib Radiographs

Thirty-eight percent of individuals with NBCC had rib anomalies which included bifid ribs, marked widening of the anterior ends of the ribs, fusion and modelling defects of the ribs. The third, fourth and fifth ribs were predominantly involved; however, abnormalities were occasionally seen in other ribs. There was no difference between the groups in the incidence of cervical and absent/rudimentary ribs.

Spine Radiographs

Scoliosis was observed more frequently in affected individuals; however, this difference was not significant. Several affected individuals however were noted to have more severe scoliosis, which was often at the site of developmental abnormalities such as hemivertebrae or fusion of the vertebral bodies. Spina bifida occulta was not observed more frequently in the NBCC population compared to the unaffected individuals.

TABLE II. Comparison of Means of Measurements in Individuals >18 Years*

Sex	Males				Females			
Status	Affected	Unaffected	Spouse		Affected	Unaffected	Spouse	
Number of persons	30	18	11	P	42	29	14	P
Height	180.5	175.6	173.1	0.03	172.4	164.8	162.7	<0.01
Head circumference	59.4	57.4	56	<0.01	57.8	55.2	55.2	<0.01
Middle finger length	8.7	8.1	7.8	<0.01	8.1	7.8	7.8	0.04
Hand length	21	20	19.6	<0.01	18.8	17.5	17.9	<0.01
Eye measurements								
Inner-canthal	3.6	3.2	3.3	<0.01	3.3	3.1	3	0.04
Inter-pupillary	6.9	6.3	6.3	0.02	6.4	6	6	<0.01
Outer-canthal	10	9.5	9.4	0.03	9.4	8.8	8.7	<0.01
Ratio upper/lower segment	0.9	1	1	0.3	0.9	0.9	0.9	0.77
Ratio middle finger/hand	0.4	0.4	0.4	0.75	0.4	0.4	0.4	0.23

*All measurements in cm.

Limbs

Flame shaped lucencies reported previously in NBCC [Dunnick, 1978] were seen on 24/80 (30%) hand films, and on 9/53 (17%) foot films. No flame shaped lucencies were observed in the unaffected persons. Polydactyly of the feet was observed in one child and was reported in one affected woman who had previous corrective surgery for this anomaly.

CT/MRI Studies

Abnormalities of the cerebrum were found in 18/42 (42.8%). Findings are reported in Table III. Falx and tentorial calcification was more easily visible on CT scans compared to skull films. In 2/10 persons with asymmetric or dilated ventricles, findings were secondary to neurosurgery and in the remaining individuals were related to communicating mild hydrocephalus. Cerebral atrophy was present in 10% and dysgenesis or agenesis of the corpus callosum in a further 10%. These individuals did not have any other detectable anatomical abnormalities of the cerebrum. The individual referred to above with medulloblastoma had neurological symptoms and signs attributable to multiple meningiomas as seen on MRI.

PROBANDS VERSUS NON-PROBANDS

The frequency of the various manifestations of NBCC in the probands (n = 26) was compared with non-probands with NBCC (n = 79). Anomalies found to be more prevalent among probands ($P = <.05$) were the more visible changes of NBCC, for example, the frequency of BCCs (in whites only), pits, frontal bossing, macrocephaly, and pectus deformity. Other defects, in particular the frequency of jaw cysts, hypertelorism, Sprengel deformity, height and radiological signs associated with NBCC were not found to be significantly increased in the probands. BCCs were also observed more frequently among probands than non-probands (approximately 2:1) among African-Americans. However, this difference was not significant (data not shown).

INDETERMINATE CASES

Of the 3 cases in this group, two individuals were under the age of 20 years and had not developed the clinical manifestations of NBCC. The youngest was a 5-year-old boy with a large head, "coarse face", bifid uvula and ptosis who had not developed other signs of NBCC. His 4-month-old brother had severe bilateral clefting of the lip and palate, macrocephaly and "coarse face" and his mother had both major and minor traits of NBCC. A 17-year-old woman who was shown to be a definite gene carrier by linkage analysis, had some facial characteristics and hypodontia with 13 congenitally absent teeth. However, she did not fulfill the criteria for the diagnosis of NBCC used in this study. A 33-year-old African-American man had a radiolucency in his jaw when evaluated at the NIH and no other definite findings of NBCC. This individual refused further medical follow-up.

FAMILY STUDIES

Considerable variation in the clinical expression of NBCC was observed within families. In the largest family evaluated with 18 affected individuals, 17 developed their first BCC at ages ranging from 8 to 35 years and 16 developed their first jaw cyst at ages ranging from 7 to 67 years. The frequency of other major signs (e.g., number of pits, presence of bifid ribs, and vertebral anomalies) also varied among relatives. Inter-familial variation was difficult to ascertain because of the enormous intra-familial variation and the small size of many families. Statistical comparisons were made between the two largest families comprising more than 10 affected relatives. Syndactyly of the second and third toes was found to consegregate with NBCC in one large family. Fourteen of the 18 affected individuals in this large family had syndactyly compared to 1/19 unaffected members ($P<0.01$). By contrast, in the other large family, only 1 of 12 affected and none of the 11 unaffected relatives had syndactyly of the second and third toes. Other defects that were significantly different ($P<0.05$) in these two families were the frequencies of strabismus and bridging of the sella. All other clinical and radiological anomalies were prevalent at similar frequencies.

The effect of genomic imprinting assessed by comparing the frequency of clinical signs of NBCC in affected individuals who had inherited the gene from their fathers versus those who had inherited it from their mothers showed that there were no significant

TABLE III. Radiological Findings in Affected Persons vs. Unaffected Relatives

	Affected N (%)	Unaffected N (%)	P
Chest and ribs			
Bifid ribs	21/82 (26)	0/32 (0)	<0.01
Splayed/fused ribs	13/82 (16)	0/32 (0)	<0.01
Cervical ribs	3/80 (4)	2/36 (6)	0.65
Absent/rudimentary ribs	5/82 (6)	2/32 (6)	0.13
Skull			
Falx calcification	53/82 (65)	2/38 (5)	<0.01
Tentorium cerebellum calcification	16/82 (20)	0/35 (0)	<0.01
Bridged sella	57/84 (68)	9/35 (26)	<0.01
Spine			
Scoliosis	23/75 (31)	5/33 (15)	0.09
Hemivertebrae	11/74 (15)	0/31 (0)	0.02
Fusion of the vertebral bodies	7/73 (10)	0/30 (0)	0.08
Spina bifida occulta	14/75 (19)	4/32 (13)	0.44
Hands and feet			
Flame shaped lucencies-hand	24/80 (30)	0/28 (0)	<0.01
Flame shaped lucencies-feet	9/53 (17)	0/8 (0)	0.2
Brain CT or MRI			
Asymmetric ventricles	10/42 (24)	0/2 (0)	ND*
Cerebral atrophy	4/42 (10)	0/2 (0)	ND
Dysgenesis/agenesis corpus callosum	4/42 (10)	0/2 (0)	ND
Meningioma	2/42 (5)	0/2 (0)	ND

*ND = *P* values not calculated.

differences in the frequency of clinical anomalies in the 2 groups. Frontal bossing was seen more frequently among individuals who had inherited NBCC from their mothers (14/36) compared to those who had inherited NBCC from their fathers (7/48) ($P = 0.02$). Other neoplasms, in particular jaw cysts, ovarian fibromas or medulloblastomas, also were not more frequent in one group.

Anticipation, assessed by comparing the frequency of manifestations in the parent generation with the child generation, indicated that there was a higher frequency of palatal abnormalities, such as high arched palate, among the offspring group (28/60) compared to the parent group (12/60) ($P = 0.01$). Cleft palate was observed in 3 offspring. There was an increased frequency of Sprengel deformity in the offspring group (9/62) compared to the parent group (3/59) but this difference was not statistically significant ($P = 0.08$). No significant differences in the two groups in the incidence of other physical or radiological traits of NBCC was observed.

COMPARISON WITH OTHER LARGE STUDIES (TABLE IV)

The diagnostic criteria used by Shanley et al. [1994] were modifications of those used by Chenevix-Trench et al. [1993]. In Evans' study [1993] similar major but fewer minor criteria were used. Given the extreme variation in expression of NBCC, and the different diagnostic criteria used, the 3 studies are remarkably similar in the distribution of the major and minor characteristics. The frequency of BCCs in the UK population over the age of 20 years was lower, but this difference was not significant ($P = 0.05$). More frequent palmar/plantar pitting in the NIH population was found compared to the UK group ($P = 0.01$); however, differences were not significant when compared with the Australian study. More frequent falx calcification in the Australian study was reported compared to the frequency in the NIH study ($P = <0.01$). Frequency of falx calcification was not reported in the UK study.

DISCUSSION

We have examined the clinical and radiological data of 105 persons with NBCC. Characteristics seen in more than 50% of individuals with NBCC are pits, BCCs, jaw cysts and falx calcification; these anomalies are included as major criteria. At least 2 of these major criteria of NBCC were found in 100/105 persons in our study. The remaining 5/105 individuals ranged in ages from 9 months to 21.5 years. Bifid ribs were seen in 3 of these individuals and the presence of 2 or more minor signs of NBCC (hemivertebrae in 1, macrocephaly in 2, hypertelorism in 2, telecanthus and frontal bossing in 1) helped in establishing the diagnosis in the remaining two individuals at age 6 and 9 years.

Diagnostic criteria used initially for recruitment can be modified based on the results of our study. Our suggested criteria for the diagnosis of NBCC is listed in Table V. Bifid/splayed/synostosed ribs, which were seen in 42% of affected individuals, may be considered a major criterion of great help in establishing a diagnosis particularly in the pediatric population. The frequency of bifid ribs in the general population is very low, having been reported as 3 to 6.2 per 1,000 [Etter, 1994; Strong, 1977].

The increased frequency of BCCs in whites (80%) compared to African-Americans (38%) has been reported in other studies [Anderson et al., 1967; Goldstein et al., 1994]. The lower frequency of BCCs in the African-American group may be related to increased protection from ultraviolet light because of the skin pigmentation. The role of sun exposure in the development of BCCs in white persons with NBCC was evalu-

TABLE IV. Comparison of Anomalies of NBCC Among Three Studies

	Evans et al. (United Kingdom)	Shanley et al. (Australia)	NIH study (United States)
Number of cases	84	118	105
Number of families	29	64	26
Mean age (Y)		35	34.5
Sex ratio M:F	1:1.3	1:1.3	1:1.2
Number with BCCs-total (%)	33/70 (47)	90/118 (76)	71/90 (80)[a]
Age >20 Y (%)	33/45 (73)	71/84 (85)	58/64 (91)[a]
Age >40 Y (%)	19/21 (90)	35/37 (95)	34/35 (97)[a]
Mean age first BCC (Y)		20.3	21.4
Number with jaw cysts-total (%)	46/70 (66)	85/113 (75)	78/105 (74)
Age >20 Y (%)	37/45 (82)	66/82 (80)	60/74 (81)
Age >40 Y (%)	19/21 (90)	25/35 (71)	29/38 (76)
Range of total number of jaw cysts (mean)	NA	1–28 (6)	1–28 (5.1)
Mean age first jaw cyst (Y)	NA	15.5	17.3
Pitting-palms/soles (%)	50/70 (71)	82/103 (80)	89/102 (87)
Cleft lip/palate (%)	4/70 (5)	4/107 (4)	3/103 (3)
Calcification of falx cerebri (%)	NA	81/89 (92)	53/82 (65)
Medulloblastoma (%)	3/84 (4)	1/118 (1)	4/105 (4)
Ovarian fibromas (%)	6/25 (24)	9/63 (14)	9/52 (17)

[a]Restricted to whites.

ated by Goldstein et al. [1993] by questionaire. They reported that 88% of BCCs in women and 86% in men from the general population occurred in sun-exposed areas of the body versus 59% in women and 65% men with NBCC. They concluded that the anatomic site distribution suggested that sun may not be an essential factor in the development of BCCs. The increased frequency in the sun-exposed areas however, suggested that sun may exacerbate the development of BCCs. They reported no significant correlation between total number of BCCs and recall of hours of lifetime sun exposure.

Palmar pits were found to be the most prevalent sign of NBCC, seen at approximately the same frequency in all age groups, therefore representing a very useful diagnostic trait of NBCC even at an early age. The incidence of pits appeared to be higher in our study than some others. The reason for this difference is unexplained but interfamilial variation is a possibility.

TABLE V. Diagnostic Criteria for NBCC Syndrome

Diagnosis of NBCC made in the presence of two major or one major and two minor criteria:

Major criteria

1. More than 2 BCCs or one under the age of 20 years
2. Odontogenic keratocysts of the jaw proven by histology
3. Three or more palmar or plantar pits
4. Bilamellar calcification of the falx cerebri
5. Bifid, fused or markedly splayed ribs
6. First degree relative with NBCC syndrome

Minor criteria

Any one of the following features:

1. Macrocephaly determined after adjustment for height
2. Congenital malformations: cleft lip or palate, frontal bossing, "coarse face," moderate or severe hypertelorism
3. Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
4. Radiological abnormalities: Bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame shaped lucencies of the hands or feet
5. Ovarian fibroma
6. Medulloblastoma

No medulloblastoma occurred after the age of 3 years in this study. Evans et al. [1991] reviewed the literature and reported an average age of diagnosis of 2.1 years in 20 cases, the ages at diagnosis ranging from 2 months to 7 years. Thus, it is very important to screen for medulloblastoma in the early years of life in patients at risk of NBCC. Our finding of early onset of BCCs in the radiation fields (mean latency period 5 yr. after exposure to radiation) was also reported by these authors. Dinehart et al. [1991] reported 3 young patients (2 with acute lymphoblastic leukemia, and 1 with astrocytoma) who developed a BCC of the scalp 8–15 years after irradiation. The multiple meningiomas we observed in one individual (latency period 22 yr.) and the cerebellar ependymoma in another (latency period 2 yr.) was likely related to the radiation therapy for medulloblastoma. Radiation-induced second intracranial neoplasms, in particular multiple meningiomas and ependymomas have been reported in other studies [Iacono et al., 1981; Anderson and Treip, 1984; Moss et al., 1988; Mack and Wilson, 1993]. The average latency period from radiation therapy to diagnosis of a meningioma was 24 ± 10 yr in the general population [Mack and Wilson, 1993].

The lower incidence of macrocephaly in our population compared to that of Shanley et al. [1994] may have occurred because we adjusted for height in our study. NBCC was previously shown to be associated with macrocephaly in probands while non-probands were not found to have significantly greater head circumferences than predicted [Bale et al., 1991]. Analysis of our data which included the 40 individuals reported by Bale et al. and an additional 27 persons with NBCC over the age of 20 yr. also showed that probands had a higher frequency of macrocephaly than other affected individuals in the families ($P < 0.01$).

The most frequent radiological sign of NBCC among affected individuals at all ages was falx calcification

(65%), the incidence increasing with age. Dunnick et al. [1978] found calcification of the falx in 85% individuals studied radiologically, and Shanley et al. [1994] reported an incidence of 92%. A bridged sella was seen in 68% of affected individuals, but also in 26% of unaffected relatives and, therefore was not found to be a discriminating sign for NBCC. Its frequency in the general population is reported to be 7% [Heublain, 1946]. In the current study, rib anomalies were seen in 43% of the affecteds which is comparable to other studies [Shanley et al., 1994; Dunnick et al., 1978]. The finding of increased frequency of developmental abnormalities involving ribs 3 to 5 in this study is interesting. Vertebral anomalies such as hemivertebrae and fusion of the vertebral bodies were seen in 31% of affected persons similar to the report by Dunnick et al. [1978]. Flame shaped lucencies of the hands were seen in 30% in our study and in 46% in the Dunnick study. The incidence of polydactyly (3%) was similar to that obtained by Shanley et al. [1994].

Absent or abnormal corpus callosum was seen as an autopsy finding in the first reported case of NBCC [Binkley and Johnson, 1951]. Other associated anomalies such as asymmetric ventricles (not associated with tumors or surgery) and cerebral atrophy have not previously been reported. Falx and tentorial calcification was seen at an earlier age on CT evaluation of the cerebrum compared to X-rays. However, in view of the exposure to radiation resulting from CT examination this investigation is no longer routinely done. MRI studies are recommended instead for detection of medulloblastomas in children.

On comparing the age of first BCC, age of first jaw cyst and frequency of anomalies in several generations of our large multi-generational families we found no evidence of anticipation. Similarly the incidence of anomalies in individuals who had inherited NBCC either from their mother or father was compared and not found to be statistically different (except for a higher frequency of frontal bossing in offspring of affected mothers). These findings contrast with the results of Shanley et al. [1994]. We found extensive intra-familial and inter-familial clinical variability which makes this type of analysis extremely difficult.

Anomalies previously reported to be associated with NBCC such as a metacarpal sign, hypospadias, cryptorchidism, anosmia and radiological features such as spina bifida occulta, and scoliosis [Gorlin, 1987] were not found to be significantly increased in affected persons compared to the two control groups in our study. For example, a metacarpal sign was seen in 10% affected and 6% of unaffected persons, these rates being close to the reported rate of 10% metacarpal sign in the general population [Bloom, 1970].

In summary, our study of 105 affected individuals and their unaffected relatives indicated that the frequency of the findings of NBCC in the US population was very similar to those obtained in other population groups (British and Australian) [Evans et al., 1993; Shanley et al., 1994]. Children proved the greatest challenge in making a diagnosis of NBCC as several of the signs of the syndrome develop over time, in particular the jaw cysts, BCCs, calcification of the falx cerebri and ovarian fibromas. Evaluation for palmar and plantar pits and radiological anomalies such as bifid ribs may prove useful indicators of NBCC.

RECOMMENDATIONS

A child who is at risk for having inherited the gene for NBCC should have careful physical evaluation at birth for pits and minor features of NBCC and radiological evaluation with rib, skull, and spine films to look for skeletal abnormalities such as bifid, fused or accessory ribs, hemivertebrae or fused vertebrae. The risk of developing a medulloblastoma in our study is greatest between 2–3 years; however has occurred up to age 7 yrs [Evans et al., 1991]. Therefore, careful regular neurological surveillance at 6 month intervals in addition to annual MRI of the cerebrum is strongly recommended up to age 7 years. Early detection would facilitate more complete surgical eradication of the tumor. In our study we do not report any cases of cardiac fibromas. Evans et al. [1993] report an incidence of 3% of cardiac fibroma in NBCC. Therefore echocardiographic evaluation is recommended at birth for a baby at risk and subsequently on clinical suspicion. Although most individuals develop their first BCC in their early 20s, children as young as 1.5 years in the absence of radiation therapy have been noted to have BCCs. Therefore regular dermatological surveillance from an early age with the frequency of visits increasing as needed during and after adolescence is important. Advising patients to reduce exposure to ultraviolet radiation may lessen their risk of developing BCCs. Radiation therapy should be avoided in NBCC if at all possible because BCCs are much more frequent and aggressive in the radiation fields and the risk of other secondary tumors is also increased. Since keratocysts of the jaw can develop as early as 4 years, regular early dental surveillance with annual panorex films is recommended as soon as the child can comply with the examination procedure. Complete removal of the cysts is essential because of the high rate of recurrence. Ovarian fibromas generally develop in the teen years; however they have been reported as early as 3.5 years. Most of these ovarian fibromas are asymptomatic and almost never become malignant. Initial ultrasound evaluation at the pre-teen stage is recommended, and repeated examination should occur if the individual becomes symptomatic.

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